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(71) Applicant : **JOHNSON & JOHNSON MEDICAL, INC.**
**2500 Arbrook Boulevard**
**Arlington Texas 76014 (US)**

(72) Inventor : **Rosenthal, Arthur L.**
**3020 Arbor Oaks**
**Arlington, Texas 76006 (US)**
Inventor : **Light, Nicholas D.**
**Glenisla, 10 Balkerach Street**
**Doune, Perthshire (GB)**
Inventor : **Haynes, Carla A.**
**35 Brownside Road**
**Cambuslang, Glasgow, G72 8NH (GB)**

(74) Representative : **Fisher, Adrian John et al**
**CARPMAELS & RANSFORD 43 Bloomsbury Square**
**London WC1A 2RA (GB)**

(54) **Heteromorphic sponges containing active agents.**

(57) The invention provides wound dressing and/or implant materials comprising a matrix structure of sponge, at least one substructure and at least one pharmacologically active agent, wherein both the matrix structure and the substructure are formed from bioabsorbable biopolymer materials. The substructure may, for example, comprise biopolymer films, flakes, fibres or microspheres embedded in the matrix structure of sponge. The pharmacologically active agent may comprise antiseptics, antibiotics, analgesics. One or more such active agents may be incorporated separately into the matrix and/or the substructure so as to achieve controlled or phasic release of the active agents into the wound.

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The present invention relates to bioabsorbable wound implant materials, and more particularly to heteromorphic sponge materials containing one or more pharmacologically active agents, which are suitable for use as implantable materials in wound repair.

Porous materials formed from synthetic and/or naturally occurring bioabsorbable materials have been used in the past as wound dressings or implants. The porous material provides structural support and a framework for tissue ingrowth while wound healing progresses. Preferably, the porous material is gradually absorbed as the tissue around the wound regenerates.

Typical bioabsorbable materials for use in the fabrication of porous wound dressings or implants include synthetic bioabsorbable polymers such as polylactic acid or polyglycolic acid, and also biopolymers such as the structural proteins and polysaccharides. The structural proteins include collagen, elastin, fibronectin, laminin and fibrin, as well as other proteins of the human connective tissue matrix. Of these, the most studied material has been collagen.

Collagen is the most abundant animal protein and the major protein of skin and connective tissue. A high degree of homology exists between the various types of collagen found in different animal species and human collagen. Accordingly, animal collagen types such as bovine collagen are useful because they exhibit very low immunogenicity when implanted into humans or used as topical dressings on human wounds.

Collagen may be prepared in a variety of physical forms including fibres, flakes, films or aqueous gels. Freeze drying an aqueous gel or an aqueous suspension of collagen may be used to produce a porous collagen sponge. Collagen sponges are described, for example, in Chvapil, J. Biomed. Mater. Res. 11 721-741 (1977). The use of collagen sponges and/or other freeze-dried biopolymer sponges as wound dressings or implant materials is disclosed, for example, in US-A-4614794 and US-A-4320201.

High molecular weight polysaccharides of the mammalian connective tissue matrix have also been used in various types of wound dressing or "synthetic skins". Yannas I.V. & Burke, J.F., J. Biomed. Mater. Res. 14 56-81 (1980) describe the use of such polysaccharides in wound dressings formed by freeze drying as sponges. High molecular weight polysaccharides include such molecules as chondroitin sulphate, hyaluronic acid and dermatan sulphate.

US-A-4614794 describes the use of other naturally occurring polysaccharide materials, especially of plant origin, in the dressing of wounds. These include, for example, alginates, chitosan, chitin, guar gum, and various plant gums.

Porous materials comprising more than one kind of bioabsorbable polymer have also been suggested for use as wound implants or wound dressings. For example:

GB-A-2215209 (Osmed Inc.) describes a biodegradable, osteogenic bone-graft substitute comprising: (a) a porous, rigid structure formed from a biodegradable polymer such as polylactic or polyglycolic acid; (b) a chemotactic substance such as hyaluronic acid, fibronectin or collagen dispersed in the interstices of the rigid structure, and (c) a biologically active or therapeutic substance such as bone morphogenetic protein evenly distributed throughout the volume of the bone-graft substitute. In use, the material is implanted into a bone defect. The material helps to restore functional architecture and mechanical integrity of the bone, initiate osteogenesis, and maintain the biological processes of bone growth while simultaneously being slowly bioabsorbed by the host organism.

JP-A-03023864 (Gunze KK) describes a reinforced collagen sponge for use as a filling material for biological tissue. The collagen sponge is reinforced by the addition of fibres of poly-(L-lactic acid). The resulting fibre-reinforced composite sponge is stronger than pure collagen or cross-linked collagen sponges, and is bioabsorbed more slowly in a host organism.

Implants made from biological, bioabsorbable components are normally intended to be invaded by the cells of the host or recipient of the implant. Cellular invasion of homogeneous sponge implants, however, is not necessarily achieved in the most efficient manner. The closed honeycomb nature of sponges presents a series of "walls" to cells invading the structure, each of which has to be breached before progress can continue. Cellular invasion is required by cells which can degrade the implant materials and by those which can lay down the tissue to replace the implant and thus repair any defect which the implant is intended to repair. Failure of either type of cell to invade the structure of the implant in an efficient manner prevents vascularisation which is required for new tissue to be able to sustain its life.

Furthermore, the porous bioabsorbable implants that have been suggested to date are all isotropic materials. That is to say, the structure and composition of the materials are uniform in all directions. Any active agents for wound healing are incorporated uniformly into the existing materials. This in turn means that the active agents are released uniformly into the wound at a rate determined only by the rate at which the implant material biodegrades. In practice, it would be preferable to have controlled or phasic release of active agents. For example, an initial rapid release of the active agents to establish a sufficient concentration of those agents at the wound surface followed by the slower release required to maintain a constant concentration. Alternatively, it may be desirable to have an initial rapid release of antiseptic followed by slower release of wound healing factors such as cytokines, FGF etc.

Accordingly, it is an object of the present inven-

tion to provide a porous bioabsorbable material that is suitable for use in the repair of full and partial thickness defects of the skin and defects or deficiencies of other soft tissues. In particular, it is an object of the present invention to provide a porous material that is readily invaded by cells of the host organism and that provides for controlled or phasic release of pharmacologically active agents into the wound.

The present invention provides a bioabsorbable heteromorphic sponge comprising a matrix structure of sponge and at least one substructure, wherein the matrix and the substructure are formed of bioabsorbable materials and the sponge comprises at least one pharmacologically active agent.

The term "heteromorphic" means that the sponges according to the present invention are structurally inhomogeneous due to the presence of the substructure in the sponge matrix. The sponges according to the present invention may also be chemically inhomogeneous if the substructure has a different chemical composition than the sponge matrix. In preferred embodiments one or more active agents is incorporated separately into the matrix structure or into one or more of the substructures. More preferably, different active agents are incorporated separately in the matrix structure and in the one or more substructures. This arrangement provides for phasic release of the different active agents because, under physiological conditions, release of the active agents takes place first from the sponge matrix and then from the substructures. Moreover, because the ratio of surface area to volume of the substructures can be controlled, the rate of release of the active agents from the substructures can thereby also be controlled.

The pharmacologically active agent is preferably selected from the group consisting of: antimicrobials to control infection, cytokines and growth factors to enhance healing; antibodies to specific wound components such as TGF β to prevent contracture, peptides to act as chemotactic agents, angiogenic factors, hormones, enzymes, metabolic or breakdown products of biopolymers, pain killers or mixtures thereof.

The amount of the pharmacologically active agent that can be incorporated will depend on the physical state of the active agent, i.e. whether it is a solid, liquid or emulsion under the conditions of incorporation. The amount that can be incorporated also depends on the chemical affinity between the active agent and the biopolymer of the matrix structure or the substructure. In favourable cases, such as when the active agent is an emulsified oil distributed in a collagen matrix, up to 90% of the weight of the matrix structure or the substructure may consist of the active agent. Likewise, up to 50% by weight of the antiseptic chlorhexidine gluconate can be incorporated into a collagen-based sponge matrix or a collagen-based substructure.

The amount of the pharmacologically active agent that is actually incorporated into the heteromorphic sponges in practice will depend on the pharmacological activity and the cost of the active agent. Thus, expensive and highly active substances such as cytokines may be incorporated at the 0.1-100 ppm by weight level. On the other hand, antiseptics such as chlorhexidine gluconate are preferably incorporated at high levels such as 1-40 percent by weight.

The substructure in the heteromorphic sponge according to the present invention may be oriented. That is to say, the substructure may be anisotropic and thereby define preferred directions for cellular ingrowth into the sponge. The anisotropy is normally provided by the use of oriented flakes, films, fibres or the like to form the substructure.

The sponge is bioabsorbable in that it is capable of full degradation and resorption within a patient's body. The heteromorphic sponge is preferably used as a wound implant for example in partial or full thickness skin injury or in tissue insufficiency where soft tissues are required to be replaced.

Preferably, the matrix and the substructure are both formed from biodegradable biopolymer materials.

The matrix is preferably strong and resilient enough to resist collapse and may be cut and/or formed so as to conform to a wound shape so that it protects and/or fills a wound bed. It may, for example, be cut so as to fill the full depth of a wound or tissue deficient area.

A heteromorphic sponge which has been cut to shape can then be placed into a debrided wound bed. A wound which has a heteromorphic sponge implanted therein may then be dressed with a suitable dressing and healing allowed to take place. Regrowth of new tissue into the heteromorphic sponge enhances wound healing.

The heteromorphic sponge may allow wound fluid, oxygen and other gases to pass through the sponge and can be replaced by host tissues in such a way that healing is promoted and cosmetic damage minimised.

Preferably, the sponge matrix comprises one or more proteins or one or more polysaccharides, or a mixture of one or more proteins with one or more polysaccharides.

The sponge matrix and substructures within the matrix may include all collagen types, tenascin, laminin, chondroitin sulphate, hyaluronic acid, dermatan sulphate, heparin sulphate, heparin, elastin, fibrin, fibronectin, vitronectin, dextran, or oxidised regenerated cellulose.

In particularly preferred embodiments, the sponge matrix consists essentially of collagen. The collagen may be provided by harvesting it as a fibrous mass containing largely collagen types I and III from such animal sources as skin, tendon, intra-organ con-

3. A bioabsorbable heteromorphic sponge according to claim 1 or 2 wherein the bioabsorbable biopolymer materials comprise macromolecules selected from the group consisting of all collagen types, elastin, fibronectin, vitronectin, laminin, tenascin, hyaluronic acid, chondroitin sulphate, dermatan sulphate, heparan sulphate, fibrin, oxidised regenerated cellulose, dextran and mixtures thereof.

4. A bioabsorbable heteromorphic sponge according to any preceding claim wherein the said at least one pharmacologically active agent is incorporated separately into the matrix structure or into the said at least one substructure.

5. A bioabsorbable heteromorphic sponge according to any preceding claim comprising a first pharmacologically active agent incorporated separately in the matrix structure of sponge and a second pharmacologically active agent different from said first pharmacologically active agent incorporated separately in the said at least one substructure.

6. A bioabsorbable heteromorphic sponge according to any preceding claim wherein the said at least one pharmacologically active agent is selected from the group consisting of antimicrobials, cytokines, growth factors, growth factor antagonists, antibodies, peptides, angiogenic factors, hormones, enzymes, metabolic or breakdown products of biopolymers, pain killers and mixtures thereof.

7. A method of making a bioabsorbable heteromorphic sponge comprising:

providing a first biopolymer component and at least one second biopolymer component;

adding a pharmacologically active agent to the first biopolymer component or to the second biopolymer component;

adding the second biopolymer component to the first biopolymer component;

forming a heterogeneous premix comprising the first biopolymer component and the second biopolymer component dispersed in a liquid; and

freeze-drying the heterogeneous premix to form the heteromorphic sponge.

8. A method according to claim 7 wherein the said at least one second biopolymer component is selected from the group consisting of milled freeze-dried sponges, powders, films, flaked or broken films, aggregates, microspheres, fibres, fibre bundles and mixtures thereof.

9. A method according to claim 7 or 8 wherein the first biopolymer component and the said at least one second biopolymer component comprise biopolymers selected from the group consisting of all collagen types, elastin, fibronectin, vitronectin, laminin, tenascin, hyaluronic acid, chondroitin sulphate, dermatan sulphate, heparan sulphate, fibrin, oxidised regenerated cellulose, dextran and mixtures thereof.

10. A method according to claim 7, 8 or 9 wherein the pharmacologically active agent is selected from the group consisting of antimicrobials, cytokines, growth factors, growth factor antagonists, antibodies, peptides, angiogenic factors, hormones, enzymes, metabolic or breakdown products of biopolymers, pain killers and mixtures thereof.

11. A method according to any of claims 7 to 10 wherein the liquid comprises water.

12. A method according to any of claims 7 to 11 wherein the heterogeneous premix is a gel, paste, slurry or emulsion.

13. A method according to any of claims 7 to 12 wherein the heterogeneous premix further contains dissolved acid in an amount sufficient to provide a pH of the heterogeneous premix between 2 and 6.

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# EUROPEAN SEARCH REPORT

Application Number
EP 93 30 2319

## DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document with indication, where appropriate, of relevant passages | Relevant to claim | CLASSIFICATION OF THE APPLICATION (Int. Cl.5) |
|---|---|---|---|
| X | EP-A-0 403 650 (TERUMO KK)<br>* page 6, line 13 - line 35 *<br>* page 9 *<br>* page 11, line 18 - line 30; claims * | 1-4 | A61L15/64<br>A61L15/44<br>A61L25/00 |
| X | US-A-3 823 212 (MILOS CHVAPIL ET AL.)<br>* examples * | 1-4 | |
| X | EP-A-0 314 109 (UNIVERSITY OF MEDICINE AND DENTISTRY OF NEW JERSEY)<br>* the whole document * | 1-3 | |
| X | WO-A-8 504 413 (UNIVERSITY OF MEDICINE AND DENTISTRY OF NEW JERSEY)<br>* claims * | 1-3 | |
| A | GB-A-1 144 552 (FMC CORPORATION)<br>* claims; examples * | 1-13 | |
| A | EP-A-0 042 253 (AVICON INC.)<br>* claims * | 1 | TECHNICAL FIELDS SEARCHED (Int. Cl.5) |
| D,A | GB-A-2 215 209 (OSMED INC.)<br>* abstract; claims * | 1 | A61L |

The present search report has been drawn up for all claims

| Place of search | Date of completion of the search | Examiner |
|---|---|---|
| THE HAGUE | 24 JUNE 1993 | M. ESPINOSA |

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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